

Amendments to the Claims:

1. (Original) A method of treating a human subject for a cancer comprising neoplastic cells expressing CD40 antigen, said method comprising administering to said subject combination therapy, said therapy comprising administration of an effective amount of an anti-CD40 antibody or antigen-binding fragment thereof in combination with an interleukin-2 (IL-2) or biologically active variant thereof, wherein said anti-CD40 antibody or antigen-binding fragment thereof is free of significant agonist activity when bound to CD40 antigen, said anti-CD40 antibody or antigen-binding fragment thereof being selected from the group consisting of:
 - a) the monoclonal antibody CHIR-5.9 or CHIR-12.12;
 - b) the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;
 - c) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:6, the sequence shown in SEQ ID NO:7, the sequence shown in SEQ ID NO:8, both the sequences shown in SEQ ID NO:6 and SEQ ID NO:7, and both the sequences shown in SEQ ID NO:6 and SEQ ID NO:8;
 - d) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequences shown in SEQ ID NO:2 and SEQ ID NO:4, and both the sequences shown in SEQ ID NO:2 and SEQ ID NO:5;
 - e) a monoclonal antibody having an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID NO:3, and both the sequences shown in SEQ ID NO:1 and SEQ ID NO:3;
 - f) a monoclonal antibody that binds to an epitope capable of binding the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;
 - g) a monoclonal antibody that binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;

h) a monoclonal antibody that binds to an epitope comprising residues 82-89 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;

i) a monoclonal antibody that competes with the monoclonal antibody CHIR-5.9 or CHIR-12.12 in a competitive binding assay;

j) the monoclonal antibody of preceding item a) or a monoclonal antibody of any one of preceding items c)-i), wherein said antibody is recombinantly produced; and

k) a monoclonal antibody that is an antigen-binding fragment of a monoclonal antibody of any one of preceding items a)-j), wherein said fragment retains the capability of specifically binding to said human CD40 antigen.

2. (Original) The method of claim 1, wherein said combination therapy provides a synergistic therapeutic effect.

3. (Original) The method of claim 1, wherein said antigen-binding fragment of said anti-CD40 antibody is selected from the group consisting of an Fab fragment, an F(ab')₂ fragment, an Fv fragment, and a single-chain Fv fragment.

4. (Original) The method of claim 1, wherein said IL-2 is human IL-2 or biologically active variant thereof.

5. (Original) The method of claim 4, wherein said variant of human IL-2 is des-alanyl-1, serine-125 human IL-2.

6. (Original) The method of claim 5, wherein said anti-CD40 antibody is the monoclonal antibody CHIR-5.9 or CHIR-12.12.

7. (Original) The method of claim 1, wherein the cancer is a B cell-related cancer or solid tumor.

8. (Original) The method of claim 7, wherein the B cell-related cancer is selected from the group consisting of non-Hodgkin's lymphoma, chronic lymphocytic leukemia, multiple myeloma, B cell lymphoma, high-grade B cell lymphoma, intermediate-grade B cell lymphoma, low-grade B cell lymphoma, B cell acute lymphoblastic leukemia, myeloblastic leukemia, Hodgkin's disease, plasmacytoma, follicular lymphoma, follicular small cleaved lymphoma, follicular large cell lymphoma, follicular mixed small cleaved lymphoma, diffuse small cleaved cell lymphoma, diffuse small lymphocytic lymphoma, prolymphocytic leukemia, lymphoplasmacytic lymphoma, marginal zone lymphoma, mucosal associated lymphoid tissue lymphoma, monocytoid B cell lymphoma, splenic lymphoma, hairy cell leukemia, diffuse large cell lymphoma, mediastinal large B cell lymphoma, lymphomatoid granulomatosis, intravascular lymphomatosis, diffuse mixed cell lymphoma, diffuse large cell lymphoma, immunoblastic lymphoma, Burkitt's lymphoma, AIDS-related lymphoma, and mantle cell lymphoma.

9. (Original) The method of claim 7, wherein said solid tumor is selected from the group consisting of urinary bladder carcinoma, breast carcinoma, liver carcinoma, gastric carcinoma, colon carcinoma, prostate cancer, renal cell carcinoma, nasopharyngeal carcinoma, squamous cell carcinoma, thyroid papillary carcinoma, melanoma, ovarian carcinoma, lung carcinoma, cervical carcinoma, and sarcomas.

10. (Original) The method of claim 1, wherein said IL-2 or variant thereof and said anti-CD40 antibody or antigen-binding fragment thereof are administered sequentially.

11. (Original) The method of claim 1, wherein said IL-2 or variant thereof and said anti-CD40 antibody or antigen-binding fragment thereof are administered simultaneously.

12. (Original) The method of claim 1, wherein said anti-CD40 antibody or antigen-binding fragment thereof is administered according to a dosing schedule selected from the group consisting of once per week, once every two weeks, once every three weeks, and once every four weeks throughout a treatment period or for a fixed duration of 4 weeks to 16 weeks within said

treatment period in combination with the administration of one or more cycles of a constant IL-2 dosing regimen during said treatment period, wherein said constant IL-2 dosing regimen comprises a first time period, wherein a constant total weekly dose of IL-2 or biologically active variant thereof is administered to said subject, and a second time period, wherein administration of said IL-2 or biologically variant thereof is withheld from said subject.

13. (Original) The method of claim 12, wherein said first time period has a duration of about 2 weeks to about 12 weeks, and wherein said second time period has a duration of about 1 week to about 4 weeks.

14. (Original) The method of claim 13, wherein said first time period has a duration of 4 weeks, and wherein said second time period has a duration of 1 week.

15. (Original) The method of claim 13, wherein a first administration of said anti-CD40 antibody or antigen-binding fragment thereof begins on day 1 of said treatment period, and wherein a first cycle of said constant IL-2 dosing regimen is initiated within 10 days of said first administration of said anti-CD40 antibody or antigen-binding fragment thereof.

16. (Original) The method of claim 15, wherein said first cycle of said constant IL-2 dosing regimen is initiated on day 8 of said treatment period.

17. (Original) The method of claim 15, wherein said treatment period comprises one or more subsequent cycles of said constant IL-2 dosing regimen that is initiated within 4 weeks following completion of said first cycle of said constant IL-2 dosing regimen or completion of any subsequent cycle of said constant IL-2 dosing regimen, wherein said administration of said anti-CD40 antibody or antigen-binding fragment thereof continues throughout said treatment period.

18. (Original) The method of claim 12, wherein said therapeutically effective dose of said anti-CD40 antibody or antigen-binding fragment thereof is in the range from about 0.5 mg/kg to about 30.0 mg/kg.

19. (Original) The method of claim 12, wherein said constant total weekly dose of IL-2 or biologically active variant thereof is administered as a single dose or is partitioned into a first series of equivalent doses that are administered according to a two-, three-, four-, five-, six- or seven-times-a-week dosing schedule.

20. (Original) The method of claim 19, wherein said IL-2 or biologically active variant thereof is administered by a route selected from the group consisting of intravenous, intramuscular, and subcutaneous.

21. (Original) The method of claim 12, wherein said constant total weekly dose of said IL-2 or biologically active variant thereof is an amount equivalent to a total weekly dose of a reference IL-2 standard administered by the same route and with the same dosing schedule, wherein said total weekly dose of the reference IL-2 standard is in a range from about 1100 μ g (18.0 MIU) to about 3300 μ g (54.0 MIU), said constant total weekly dose of said IL-2 or biologically active variant thereof providing at least 70% of the natural killer (NK) cell activity that is provided by said total weekly dose of the reference IL-2 standard.

22. (Original) The method of claim 21, wherein said total weekly dose of the reference IL-2 standard is about 1100 μ g (18.0 MIU) to about 2567 μ g (42.0 MIU), and wherein said total weekly dose of the reference IL-2 standard is partitioned into three equivalent doses that are administered according to a three-times-a-week dosing schedule.

23. (Original) The method of claim 1, wherein said anti-CD40 antibody or antigen-binding fragment thereof is administered according to a dosing schedule selected from the group consisting of once per week, once every two weeks, once every three weeks, and once every four

weeks throughout a treatment period or for a fixed duration of 4 weeks to 16 weeks within said treatment period in combination with the administration of one or more cycles of a two-level IL-2 dosing regimen during said treatment period, wherein said two-level IL-2 dosing regimen comprises a first time period, wherein a higher total weekly dose of an IL-2 or biologically active variant thereof is administered to said subject, followed by a second time period, wherein a lower total weekly dose of said IL-2 or biologically active variant thereof is administered to said subject.

24. (Original) The method of claim 23, wherein a first dose of said IL-2 or biologically active variant thereof is administered to said subject prior to administering a first dose of said antagonist anti-CD40 antibody or antigen-binding fragment thereof.

25. (Original) The method of claim 24, wherein said first dose of said IL-2 or biologically active variant thereof is administered up to one month before said first dose of said antagonist anti-CD40 antibody or antigen-binding fragment thereof is administered to said subject.

26. (Original) The method of claim 25, wherein said first dose of said IL-2 or biologically active variant thereof is administered one week before said first dose of said antagonist anti-CD40 antibody or antigen-binding fragment thereof is administered to said subject.

27. (Original) The method of claim 23, wherein a first dose of said IL-2 or biologically active variant thereof is administered to said subject concurrently with a first dose of said antagonist anti-CD40 antibody or antigen-binding fragment thereof.

28. (Original) The method of claim 23, wherein a first dose of said IL-2 or biologically active variant thereof is administered to said subject one week after a first dose of

said antagonist anti-CD40 antibody or antigen-binding fragment thereof is administered to said subject.

29. (Original) The method of claim 23, wherein said therapeutically effective dose of said antagonist anti-CD40 antibody or antigen-binding fragment thereof is in the range from about 0.5 mg/kg to about 30.0 mg/kg.

30. (Original) The method of claim 23, wherein said two-level IL-2 dosing regimen has a combined duration of 4 weeks to 16 weeks.

31. (Original) The method of claim 30, wherein said first time period of said two-level IL-2 dosing regimen has a duration of at least 1 week out of said combined duration of 4 weeks to 16 weeks.

~~34.~~32. (Currently amended) The method of claim 30, wherein said first time period of said two-level dosing regimen of IL-2 has a duration that is one-half of said combined duration of 4 weeks to 16 weeks.

~~35.~~33. (Currently amended) The method of claim 23, wherein said higher total weekly dose of said IL-2 or biologically active variant thereof is administered as a single dose or is partitioned into a first series of equivalent doses that are administered according to a two-, three-, four-, five-, six- or seven-times-a-week dosing schedule, and wherein said lower total weekly dose of said IL-2 or biologically active variant thereof is administered as a single dose or is partitioned into a second series of equivalent doses that are administered according to a two-, three-, four-, five-, six- or seven-times-a-week dosing schedule.

~~36.~~34. (Currently amended) The method of claim ~~35~~33, wherein said IL-2 or biologically active variant thereof is administered by a route selected from the group consisting of intravenous, intramuscular, and subcutaneous.

~~38~~35. (Currently amended) The method of claim ~~36~~34, wherein said first series of equivalent doses is administered according to three-times-a-week dosing schedule, and wherein said second series of equivalent doses is administered according to a three-times-a-week dosing schedule.

~~39~~36. (Currently amended) The method of claim 23, wherein:

a) said higher total weekly dose of said IL-2 or biologically active variant thereof is an amount equivalent to a higher total weekly dose of a reference IL-2 standard administered by the same route and with the same dosing schedule, wherein said higher total weekly dose of the reference IL-2 standard is in a range from about 1834 μg (30.0 MIU) to about 3300 μg (54.0 MIU), said higher total weekly dose of said IL-2 or biologically active variant thereof providing at least 70% of the natural killer (NK) activity that is provided by said higher total weekly dose of the reference IL-2 standard;

b) said lower total weekly dose of said IL-2 or biologically active variant thereof is an amount equivalent to a lower total weekly dose of the reference IL-2 standard administered by the same route and with the same dosing schedule, wherein said lower total weekly dose of the reference IL-2 standard is in a range from about 1100 μg (18.0 MIU) to about 2384 μg (39.0 MIU), said lower total weekly dose of said IL-2 or biologically active variant thereof providing at least 70% of the natural killer (NK) activity that is provided by said lower total weekly dose of the reference IL-2 standard; and

c) said lower total weekly dose of said IL-2 or biologically active variant thereof is lower than said higher total weekly dose of said IL-2 or biologically active variant thereof.

~~40~~37. (Currently amended) The method of claim ~~39~~36, wherein said higher total weekly dose of the reference IL-2 standard is about 1834 μg (30.0 MIU) to about 2567 μg (42.0 MIU) and said lower total weekly dose of the reference IL-2 standard is about 1100 μg (18.0 MIU) to about 1834 μg (30.0 MIU).

41.38. (Currently amended) The method of claim 4037, wherein said higher total weekly dose of the reference IL-2 standard is about 2567 μg (42.0 MIU), said lower total weekly dose of the reference IL-2 standard is about 1834 μg (30.0 MIU), and wherein said higher total weekly dose of the reference IL-2 standard and said lower total weekly dose of the reference IL-2 standard are each partitioned into three equivalent doses that are administered according to a three-times-a-week dosing schedule.

42.39. (Currently amended) The method of claim 23, further comprising an interruption in said two-level IL-2 dosing regimen, said interruption comprising a time period off of administration of said IL-2 or biologically active variant thereof between said first time period and said second time period of said two-level IL-2 dosing regimen.

43.40. (Currently amended) The method of claim 4239, wherein said interruption has a duration of about 1 week to about 4 weeks.

44.41. (Currently amended) The method of claim 23, wherein said treatment period comprises one or more subsequent cycles of said two-level IL-2 dosing regimen that is initiated about 1 week to about 4 weeks following completion of a first cycle of said two-level IL-2 dosing regimen or completion of any subsequent cycle of said two-level IL-2 dosing regimen, wherein said weekly administration of said antagonist anti-CD40 antibody or antigen-binding fragment thereof continues throughout said treatment period.

45.42. (Currently amended) The method of claim 4441, wherein at least one cycle of said two-level IL-2 dosing regimen comprises an interruption in said two-level IL-2 dosing regimen, said interruption comprising a time period off of administration of said IL-2 or biologically active variant thereof between said first time period and said second time period of any given cycle of said two-level IL-2 dosing regimen that comprises said interruption.

~~46-43.~~ (Currently amended) A method of treating a human subject for a cancer comprising neoplastic cells expressing CD40 antigen, said method comprising administering to said subject combination therapy, said therapy comprising administration of an effective amount of an antagonist anti-CD40 antibody or antigen-binding fragment thereof in combination with interleukin-2 (IL-2) or biologically active variant thereof, wherein said antagonist anti-CD40 antibody or antigen-binding fragment thereof specifically binds Domain 2 of human CD40 antigen and is free of significant agonist activity when bound to Domain 2 of human CD40 antigen.

~~47-44.~~ (Currently amended) The method of claim ~~4643~~, wherein said combination therapy provides a synergistic therapeutic effect.

~~48-45.~~ (Currently amended) The method of claim ~~4643~~, wherein said antagonist anti-CD40 antibody is a human antibody.

~~49-46.~~ (Currently amended) The method of claim ~~4643~~, wherein said antagonist anti-CD40 antibody is recombinantly produced.

~~50-47.~~ (Currently amended) The method of claim ~~4643~~, wherein said antagonist anti-CD40 antibody has the binding specificity of an antibody selected from the group consisting of the antibody produced by hybridoma cell line 5.9 and the antibody produced by hybridoma cell line 12.12.

~~51-48.~~ (Currently amended) The method of claim ~~4643~~, wherein said antagonist anti-CD40 antibody is selected from the group consisting of the antibody produced by the hybridoma cell line deposited with the ATCC as Patent Deposit No. PTA-5542 and the antibody produced by the hybridoma cell line deposited with the ATCC as Patent Deposit No. PTA-5543.

~~52-49.~~ (Currently amended) The method of claim ~~4643~~, wherein said antagonist anti-CD40 antibody has the binding specificity of monoclonal antibody CHIR-12.12 or CHIR-5.9.

~~53-50.~~ (Currently amended) The method of claim ~~4643~~, wherein said antagonist anti-CD40 antibody binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12.

~~54-51.~~ (Currently amended) The method of claim ~~4643~~, wherein said antagonist anti-CD40 antibody or antigen-binding fragment thereof is selected from the group consisting of:

a) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence shown in SEQ ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID NO:2 and SEQ ID NO:5;

b) a monoclonal antibody having an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;

c) a monoclonal antibody that binds to an epitope capable of binding the monoclonal antibody produced by the hybridoma cell line 12.12;

d) a monoclonal antibody that binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;

e) a monoclonal antibody that competes with the monoclonal antibody CHIR-12.12 in a competitive binding assay;

f) a monoclonal antibody of any one of preceding items a)-e), wherein said antibody is recombinantly produced; and

g) a monoclonal antibody that is an antigen-binding fragment of the CHIR-12.12 monoclonal antibody or an antigen-binding fragment of a monoclonal antibody of any one of preceding items a)-f), where the fragment retains the capability of specifically binding to said human CD40 antigen.

~~55.52.~~ (Currently amended) The method of claim ~~4643~~, wherein said antigen-binding fragment of said anti-CD40 antibody is selected from the group consisting of an Fab fragment, an F(ab')₂ fragment, an Fv fragment, and a single-chain Fv fragment.

~~56.53.~~ (Currently amended) The method of claim ~~4643~~, wherein said IL-2 is human IL-2 or biologically active variant thereof.

~~57.54.~~ (Currently amended) The method of claim ~~4653~~, wherein said variant of human IL-2 is des-alanyl-1, serine-125 human IL-2.

~~58.55.~~ (Currently amended) The method of claim ~~5754~~, wherein said antagonist anti-CD40 antibody is the monoclonal antibody CHIR-5.9 or CHIR-12.12.

~~59.56.~~ (Currently amended) The method of claim ~~4643~~, wherein said cancer is a B cell-related cancer or solid tumor.

~~60.57.~~ (Currently amended) The method of claim ~~5956~~, wherein the B cell-related cancer is selected from the group consisting of non-Hodgkin's lymphoma, chronic lymphocytic leukemia, multiple myeloma, B cell lymphoma, high-grade B cell lymphoma, intermediate-grade B cell lymphoma, low-grade B cell lymphoma, B cell acute lymphoblastic leukemia, myeloblastic leukemia, Hodgkin's disease, plasmacytoma, follicular lymphoma, follicular small cleaved lymphoma, follicular large cell lymphoma, follicular mixed small cleaved lymphoma, diffuse small cleaved cell lymphoma, diffuse small lymphocytic lymphoma, prolymphocytic leukemia, lymphoplasmacytic lymphoma, marginal zone lymphoma, mucosal associated lymphoid tissue lymphoma, monocytoid B cell lymphoma, splenic lymphoma, hairy cell leukemia, diffuse large cell lymphoma, mediastinal large B cell lymphoma, lymphomatoid granulomatosis, intravascular lymphomatosis, diffuse mixed cell lymphoma, diffuse large cell

lymphoma, immunoblastic lymphoma, Burkitt's lymphoma, AIDS-related lymphoma, and mantle cell lymphoma.

~~61-58.~~ (Currently amended) The method of claim ~~59~~56, wherein said solid tumor is selected from the group consisting of urinary bladder carcinoma, breast carcinoma, liver carcinoma, gastric carcinoma, colon carcinoma, prostate cancer, renal cell carcinoma, nasopharyngeal carcinoma, squamous cell carcinoma, thyroid papillary carcinoma, melanoma, ovarian carcinoma, lung carcinoma, cervical carcinoma, and sarcomas.

~~62-59.~~ (Currently amended) The method of claim ~~46~~43, wherein said IL-2 or variant thereof and said antagonist anti-CD40 antibody or antigen-binding fragment thereof are administered sequentially.

~~63-60.~~ (Currently amended) The method of claim ~~46~~43, wherein said IL-2 or variant thereof and said antagonist anti-CD40 antibody or antigen-binding fragment thereof are administered simultaneously.

~~64-61.~~ (Currently amended) The method of claim ~~46~~43, wherein said anti-CD40 antibody or antigen-binding fragment thereof is administered according to a dosing schedule selected from the group consisting of once per week, once every two weeks, once every three weeks, and once every four weeks throughout a treatment period or for a fixed duration of 4 weeks to 16 weeks within said treatment period in combination with the administration of one or more cycles of a constant IL-2 dosing regimen during said treatment period, wherein said constant IL-2 dosing regimen comprises a first time period, wherein a constant total weekly dose of IL-2 or biologically active variant thereof is administered to said subject, and a second time period, wherein administration of said IL-2 or biologically variant thereof is withheld from said subject.

~~65-62.~~ (Currently amended) The method of claim ~~6461~~, wherein said first time period has a duration of about 2 weeks to about 12 weeks, and wherein said second time period has a duration of about 1 week to about 4 weeks.

~~66-63.~~ (Currently amended) The method of claim ~~6562~~, wherein said first time period has a duration of 4 weeks, and wherein said second time period has a duration of 1 week.

~~67-64.~~ (Currently amended) The method of claim ~~6562~~, wherein a first administration of said anti-CD40 antibody or antigen-binding fragment thereof begins on day 1 of said treatment period, and wherein a first cycle of said constant IL-2 dosing regimen is initiated within 10 days of said first administration of said anti-CD40 antibody or antigen-binding fragment thereof.

~~68-65.~~ (Currently amended) The method of claim ~~6764~~, wherein said first cycle of said constant IL-2 dosing regimen is initiated on day 8 of said treatment period.

~~69-66.~~ (Currently amended) The method of claim ~~6764~~, wherein said treatment period comprises one or more subsequent cycles of said constant IL-2 dosing regimen that is initiated within 4 weeks following completion of said first cycle of said constant IL-2 dosing regimen or completion of any subsequent cycle of said constant IL-2 dosing regimen, wherein said administration of said anti-CD40 antibody or antigen-binding fragment thereof continues throughout said treatment period.

~~70-67.~~ (Currently amended) The method of claim ~~6461~~, wherein said therapeutically effective dose of said anti-CD40 antibody or antigen-binding fragment thereof is in the range from about 0.5 mg/kg to about 30.0 mg/kg.

~~71-68.~~ (Currently amended) The method of claim ~~6461~~, wherein said constant total weekly dose of IL-2 or biologically active variant thereof is administered as a single dose or is

partitioned into a first series of equivalent doses that are administered according to a two-, three-, four-, five-, six- or seven-times-a-week dosing schedule.

~~72.69.~~ (Currently amended) The method of claim ~~7168~~, wherein said IL-2 or biologically active variant thereof is administered by a route selected from the group consisting of intravenous, intramuscular, and subcutaneous.

~~73.70.~~ (Currently amended) The method of claim ~~6461~~, wherein said constant total weekly dose of said IL-2 or biologically active variant thereof is an amount equivalent to a total weekly dose of a reference IL-2 standard administered by the same route and with the same dosing schedule, wherein said total weekly dose of the reference IL-2 standard is in a range from 1100 μg (18.0 MIU) to 3300 μg (54.0 MIU), said constant total weekly dose of said IL-2 or biologically active variant thereof providing at least 70% of the natural killer (NK) cell activity that is provided by said total weekly dose of the reference IL-2 standard.

~~74.71.~~ (Currently amended) The method of claim ~~7370~~, wherein said total weekly dose of the reference IL-2 standard is 1100 μg (18.0 MIU) to 2567 μg (42.0 MIU), and wherein said total weekly dose of the reference IL-2 standard is partitioned into three equivalent doses that are administered according to a three-times-a-week dosing schedule.

~~75.72.~~ (Currently amended) The method of claim ~~4643~~, wherein said anti-CD40 antibody or antigen-binding fragment thereof is administered according to a dosing schedule selected from the group consisting of once per week, once every two weeks, once every three weeks, and once every four weeks throughout a treatment period in combination with the administration of one or more cycles of a two-level IL-2 dosing regimen during said treatment period, wherein said two-level IL-2 dosing regimen comprises a first time period, wherein a higher total weekly dose of an IL-2 or biologically active variant thereof is administered to said subject, followed by a second time period, wherein a lower total weekly dose of said IL-2 or biologically active variant thereof is administered to said subject.

~~76~~.73. (Currently amended) The method of claim ~~75~~72, wherein a first dose of said IL-2 or biologically active variant thereof is administered to said subject prior to administering a first dose of said antagonist anti-CD40 antibody or antigen-binding fragment thereof.

~~77~~.74. (Currently amended) The method of claim ~~76~~73, wherein said first dose of said IL-2 or biologically active variant thereof is administered up to one month before said first dose of said antagonist anti-CD40 antibody or antigen-binding fragment thereof is administered to said subject.

~~78~~.75. (Currently amended) The method of claim ~~77~~74, wherein said first dose of said IL-2 or biologically active variant thereof is administered one week before said first dose of said antagonist anti-CD40 antibody or antigen-binding fragment thereof is administered to said subject.

~~79~~.76. (Currently amended) The method of claim ~~75~~72, wherein a first dose of said IL-2 or biologically active variant thereof is administered to said subject concurrently with a first dose of said antagonist anti-CD40 antibody or antigen-binding fragment thereof.

~~80~~.77. (Currently amended) The method of claim ~~75~~72, wherein a first dose of said IL-2 or biologically active variant thereof is administered to said subject one week after a first dose of said antagonist anti-CD40 antibody or antigen-binding fragment thereof is administered to said subject.

~~81~~.78. (Currently amended) The method of claim ~~75~~72, wherein said therapeutically effective dose of said antagonist anti-CD40 antibody or antigen-binding fragment thereof is in the range from about 0.5 mg/kg to about 30.0 mg/kg.

~~82-79.~~ (Currently amended) The method of claim ~~7572~~, wherein said two-level IL-2 dosing regimen has a combined duration of 4 weeks to 16 weeks.

~~83-80.~~ (Currently amended) The method of claim ~~8279~~, wherein said first time period of said two-level IL-2 dosing regimen has a duration of at least 1 week out of said combined duration of 4 weeks to 16 weeks.

~~84-81.~~ (Currently amended) The method of claim ~~8279~~, wherein said first time period of said two-level dosing regimen of IL-2 has a duration that is one-half of said combined duration of 4 weeks to 16 weeks.

~~85-82.~~ (Currently amended) The method of claim ~~7572~~, wherein said higher total weekly dose of said IL-2 or biologically active variant thereof is administered as a single dose or is partitioned into a first series of equivalent doses that are administered according to a two-, three-, four-, five-, six- or seven-times-a-week dosing schedule, and wherein said lower total weekly dose of said IL-2 or biologically active variant thereof is administered as a single dose or is partitioned into a second series of equivalent doses that are administered according to a two-, three-, four-, five-, six- or seven-times-a-week dosing schedule.

~~86-83.~~ (Currently amended) The method of claim ~~8582~~, wherein said IL-2 or biologically active variant thereof is administered by a route selected from the group consisting of intravenous, intramuscular, and subcutaneous.

~~87-84.~~ (Currently amended) The method of claim ~~8683~~, wherein said first series of equivalent doses is administered according to three-times-a-week dosing schedule, and wherein said second series of equivalent doses is administered according to a three-times-a-week dosing schedule.

~~88-85.~~ (Currently amended) The method of claim ~~7572~~, wherein:

a) said higher total weekly dose of said IL-2 or biologically active variant thereof is an amount equivalent to a higher total weekly dose of a reference IL-2 standard administered by the same route and with the same dosing schedule, wherein said higher total weekly dose of the reference IL-2 standard is in a range from 1834 μg (30.0 MIU) to 3300 μg (54.0 MIU), said higher total weekly dose of said IL-2 or biologically active variant thereof providing at least 70% of the natural killer (NK) activity that is provided by said higher total weekly dose of the reference IL-2 standard;

b) said lower total weekly dose of said IL-2 or biologically active variant thereof is an amount equivalent to a lower total weekly dose of the reference IL-2 standard administered by the same route and with the same dosing schedule, wherein said lower total weekly dose of the reference IL-2 standard is in a range from 1100 μg (18.0 MIU) to about 2384 μg (39.0 MIU), said lower total weekly dose of said IL-2 or biologically active variant thereof providing at least 70% of the natural killer (NK) activity that is provided by said lower total weekly dose of the reference IL-2 standard; and

c) said lower total weekly dose of said IL-2 or biologically active variant thereof is lower than said higher total weekly dose of said IL-2 or biologically active variant thereof.

~~89~~86. (Currently amended) The method of claim ~~88~~85, wherein said higher total weekly dose of the reference IL-2 standard is 1834 μg (30.0 MIU) to 2567 μg (42.0 MIU) and said lower total weekly dose of the reference IL-2 standard is 1100 μg (18.0 MIU) to 1834 μg (30.0 MIU).

~~90~~87. (Currently amended) The method of claim ~~89~~86, wherein said higher total weekly dose of the reference IL-2 standard is 2567 μg (42.0 MIU), said lower total weekly dose of the reference IL-2 standard is 1834 μg (30.0 MIU), and wherein said higher total weekly dose of the reference IL-2 standard and said lower total weekly dose of the reference IL-2 standard are each partitioned into three equivalent doses that are administered according to a three-times-a-week dosing schedule.

~~91-88.~~ (Currently amended) The method of claim ~~7572~~, further comprising an interruption in said two-level dosing regimen of IL-2, said interruption comprising a time period off of administration of said IL-2 or biologically active variant thereof between said first time period and said second time period of said two-level IL-2 dosing regimen.

~~92-89.~~ (Currently amended) The method of claim ~~9188~~, wherein said interruption has a duration of about 1 week to about 4 weeks.

~~93-90.~~ (Currently amended) The method of claim ~~7572~~, wherein said treatment period comprises one or more subsequent cycles of said two-level IL-2 dosing regimen that is initiated about 1 week to about 4 weeks following completion of a first cycle of said two-level IL-2 dosing regimen or completion of any subsequent cycle of said two-level IL-2 dosing regimen, wherein said weekly administration of said antagonist anti-CD40 antibody or antigen-binding fragment thereof continues throughout said treatment period.

~~94-91.~~ (Currently amended) The method of claim ~~9390~~, wherein at least one cycle of said two-level IL-2 dosing regimen comprises an interruption in said two-level IL-2 dosing regimen, said interruption comprising a time period off of administration of said IL-2 or biologically active variant thereof between said first time period and said second time period of any given cycle of said two-level IL-2 dosing regimen that includes said interruption.

~~95-92.~~ (Currently amended) The method ~~according to any one of claims 1-94~~ of claim 1, wherein said anti-CD40 antibody or antigen-binding fragment thereof is administered intravenously or subcutaneously.

93. (New) The method of claim 43, wherein said anti-CD40 antibody or antigen-binding fragment thereof is administered intravenously or subcutaneously.